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An anti-DNA antibody prefers damaged dsDNA over native

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Abstract

© 2016 Informa UK Limited, trading as Taylor & Francis Group. DNA–protein interactions, including DNA–antibody complexes, have both fundamental and practical significance. In particular, antibodies against double-stranded DNA play an important role in the pathogenesis of autoimmune diseases. Elucidation of structural mechanisms of an antigen recognition and interaction of anti-DNA antibodies provides a basis for understanding the role of DNA-containing immune complexes in human pathologies and for new treatments. Here we used Molecular Dynamic simulations of bimolecular complexes of a segment of dsDNA with a monoclonal anti-DNA antibody's Fab-fragment to obtain detailed structural and physical characteristics of the dynamic intermolecular interactions. Using a computationally modified crystal structure of a Fab–DNA complex (PDB: 3VW3), we studied in silico equilibrium Molecular Dynamics of the Fab-fragment associated with two homologous dsDNA fragments, containing or not containing dimerized thymine, a product of DNA photodamage. The Fab-fragment interactions with the thymine dimer-containing DNA was thermodynamically more stable than with the native DNA. Th e amino acid residues constituting a paratope and the complementary nucleotide epitopes for both Fab–DNA constructs were identified. Stacking and electrostatic interactions were shown to play the main role in the antibody–dsDNA contacts, while hydrogen bonds were less significant. The aggregate of data show that the chemically modified dsDNA (containing a covalent thymine dimer) has a higher affinity toward the antibody and forms a stronger immune complex. These findings provide a mechanistic insight into formation and properties of the pathogenic anti-DNA antibodies in autoimmune diseases, such as systemic lupus erythematosus, associated with skin photosensibilization and DNA photodamage.

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Keywords

anti-DNA antibody, dsDNA, immune complex, Molecular Dynamics simulation, thymine dimer

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